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(54) Title: NON-INVASIVE IMAGING OF BIOLOGICAL TISSUE

(57) Abstract

An optical system (10) for *in vivo*, non-invasive imaging of tissue change includes an optical module (12) with an array of input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of arrayed single source, single detector pairs engaged directly with the subject; a spectrophotometer (20) including a light source constructed to introduce electromagnetic radiation of visible or infrared wavelength into the examined tissue successively at the input ports, the wavelength being sensitive to a constituent of the imaged tissue; a detector constructed to detect, at the detection ports, radiation of the selected wavelength that has migrated in the tissue from respective input ports; and a processor receiving signals of the detected radiation from the detector, and constructed and arranged to create a defined spatial image of the tissue by effectively producing from signals from the multiplicity of arrayed single source, single detector pairs, a succession of data sets representing, from a selected view, a succession of spatial images of the tissue, and an image data set related to differences between data of the successive data sets. Imaging instruments and a method are also described.
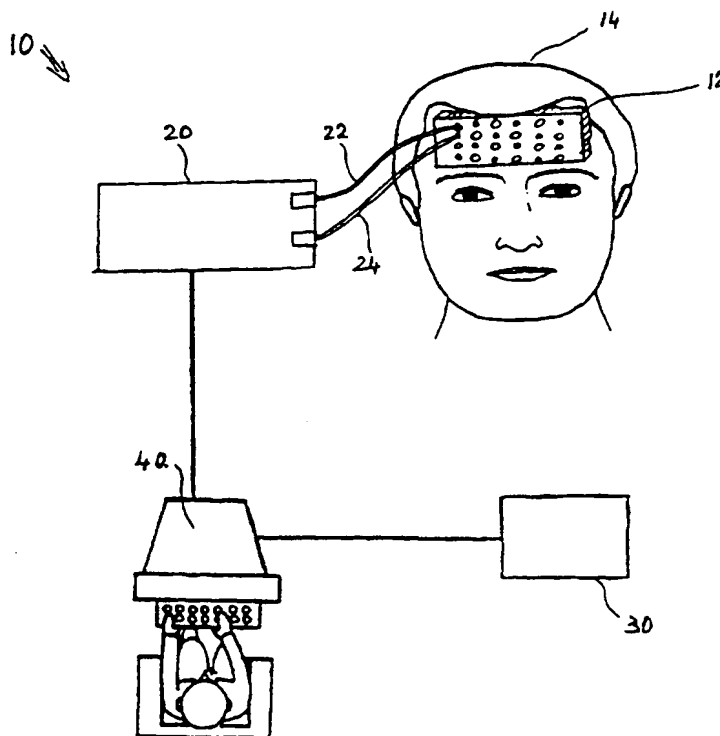
NON-INVASIVE IMAGING OF BIOLOGICAL TISSUE

The invention provides proof in principle of the practicality for medical purposes of imaging body tissue, and in particular, neural tissue, especially the brain, using spectrophotometric techniques.

Certain prior work has produced low resolution shadowgrams of the exterior of the cortex, lacking edges or defined contours.

We have shown that by employing an array of ports for a set of single source, single detector pairs, and by implementing the system to acquire a sequence of data sets, distinct difference image data sets can be realized that are useful in diagnosis and treatment, e.g. on a real time basis, with relatively low expense. Blood volume and oxygenation, for instance, can be directly imaged.

We have demonstrated in brain models and human brains, that an optical imaging device can localize the activated area of the human brain. We have produced defined images that show that single functions of the brain such as observing an object (visual), moving a small part of the body (sensory motor) and thinking (cognition) appear to activate only an area as small as 0.5 to 1 cm of the brain cortex. The place of activation observed from the produced image was where it was expected. In the case of side-by-side source and detector pair, between which the probability pattern of photons takes a banana shape, the theoretical resolution and sensitive depth depends on the source-detector distance (half of the distance). By selection of the source-detector distance, a resolution of the image as good as 1.25 cm has been obtained. Imaging of white brain matter to selected depths is realized by increasing the spacing up to 7 cm.

- 3 -

It is shown that light sources that provide no safety hazard, at relatively low cost can be usefully employed in true imaging. By employing difference measurements, the uncertainties normally limiting
5 continuous wave spectroscopy (CWS) to trend indications are avoided. The greater information content of phase modulation and time resolved spectroscopy leads to even more informative images.

According to one important aspect of the
10 invention, an optical system is provided for in vivo, non-invasive imaging of tissue change comprising   an optical module including an array of input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of arrayed single source,
15 single detector pairs engaged directly with the subject, a spectrophotometer including a light source means constructed to introduce electromagnetic radiation of visible or infra-red wavelength into the examined tissue successively at the input ports, the wavelength being
20 sensitive to a constituent of the imaged tissue, detector means constructed to detect, at the detection ports, radiation of the selected wavelength that has migrated in the tissue from respective input ports, and a processor receiving signals of the detected radiation from the
25 detector means, and constructed and arranged to create a defined spatial image of the tissue by effectively producing from signals from the multiplicity of arrayed single source, single detector pairs, a succession of data sets representing, from a selected view, a
30 succession of spatial images of the tissue, and an image data set related to differences between data of the successive data sets.

In another important aspect of the invention, an optical system is provided for in vivo, non-invasive
35 functional neuroimaging of tissue comprising   a

- 5 -

distance being selected according to the tissue depth
desired to be imaged.

The optical module or an associated set of the
modules is constructed to take readings at different
5 depths to produce 3D data sets from which an image date
set may be produced.

The processor is adapted to produce the image data
set by implementing an optical tomography algorithm.

The optical tomography algorithm preferably
10 employs factors related to determined probability
distribution of photons attributable to the scattering
character of the tissue being imaged.

The optical system is constructed to form the
image data set from a part of the head. In particular
15 embodiments the optical system is constructed to form the
functional image data set from below the surface region
of the cortex.

The stimulator is constructed to stimulate the
visual cortex, the cognitive cortex, the sensory motor
20 cortex, or spinal tissue.

In various embodiments the stimulator is
constructed to deliver electrical signals to selected
tissue, apply an electrical field to selected tissue, or
deliver magnetic signals to selected tissue.

25   In various embodiments the image set is related to
at least one of the group consisting of blood volume,
hemoglobin oxygenation or deoxygenation, photon
absorption coefficient, photon scattering coefficient,
refractive index, change in magnetic field, change in
30 electric field, production of or change of a specific
tissue constituent, and production of or change in the
concentration of a pigment.

In various embodiments the tissue constituent is
an endogenous pigment, for example hemoglobin, or an
35 exogenous pigment, for example a selected contrast agent.

In certain other embodiments the spectrophotometer includes a light source means that is constructed to generate pulses of radiation of the wavelength, the pulses having duration on the order of a nanosecond or
5 less, the detector means being constructed to detect over time photons of modified pulses that have migrated in the tissue from the input ports, an analyzer, connected to the detector means, adapted to determine a change in the pulse waveform shape of the detected pulses relative to
10 the introduced pulses, at the wavelength, and the processor being constructed and arranged to create the image data set based on the determined pulse waveform change.

Preferably, this processor is constructed and
15 arranged to calculate the effective pathlength of photons of the wavelength migrating between the input and detection ports in conjunction with creating the image data set.

In certain embodiments of this aspect of the
20 invention the processor is constructed and arranged to calculate the scattering coefficient at the wavelength in conjunction with creating the image data set.

Also, in certain embodiments, the processor is constructed and arranged to calculate the absorption
25 coefficient at said wavelength in conjunction with creating the image data set.

In preferred embodiments the optical system is constructed to introduce and detect photons at two wavelengths selected to provide sensitivity to a property
30 of the constituent.

In certain preferred embodiments, the source means of the optical system comprises an incandescent lamp, and preferably a set of miniature lamps directly contacting the subject.

source at a time enabling accumulation of single source-detector responses.

The light source or sources are incandescent lamps, LEDs, laser diodes or other lasers.

5   The instrument comprises an array of sources of near infrared or visible photons, an array of detectors positioned to receive photons from the sources in respective source-detector pairs following migration of the photons from the sources through the tissue, a system

10 enabling numerous readings of migrated photons to be taken systematically at the detectors for different source-detector positions relative to the tissue, and a processor employing an imaging algorithm based on respectively different probabilities for a given source-

15 detector position, for photons from the source passing through different regions of the volume of the scattering tissue that are located at different positions distributed laterally from a straight reference line between source and detector.

20   According to another important aspect of the invention, an instrument is provided for functional imaging of brain activity of a subject comprising an imager constructed and arranged to image hemoglobin, deoxyhemoglobin or blood volume, the imager comprising an

25 array of sources of near infrared or visible photons, and array of detectors positioned to receive photons from the sources following migration of photons from the sources through the tissue, a system enabling numerous readings of migrated photons to be taken systematically for

30 different source-detector positions relative to the tissue, and a processor employing data sets taken during rest and during stimulation, with an imaging algorithm that is based on respectively different probabilities for a given source-detector position, for photons from the

35 source passing through different regions of the volume of

subject an imaging instrument according to any of the
foregoing aspects. In certain preferred embodiments of
the methods an optical contrast agent or a drug is
introduced to the blood stream of the subject, and the
5 instrument is employed to produce an image data set for
the tissue while the contrast agent or drug is present in
blood circulating in the tissue of the subject or is
present in localized tissue.

These and other features and advantages of the
10 invention will be understood from the drawings, the
following description of preferred embodiments and the
claims.

Brief Description of the Drawings

Fig. 1 depicts a block diagram of an optical
15 tomography system for imaging functional activity of the
brain.

Fig. 2 depicts a diagram of an optical module
employed in one preferred embodiment of the system of
Fig. 1.

20 Fig. 2A depicts a schematic circuit diagram of a
continuous wave spectrophotometer employed in one
preferred embodiment of the system of Fig. 1.

Figs. 3A and 3B depict differential images of
blood volumes detected on the visual cortex of a man
25 watching a monitor screen and after a rest period of 2
minutes, respectively.

Figs. 4A, 4B and 4C depict differential images of
blood volumes of the motor cortex of a man tapping his
fingers, after a rest period of 30 seconds, and restored
30 rest volumes at 30 - 60 seconds, respectively.

Figs. 5A, 5B and 5C depict differential images of
the hemoglobin oxygenation of the prefrontal cortex of a
man translating words from English to French.

component, that absorbs superficial photons not propagating in the examined tissue.

Spectrophotometer unit 20 is a continuous wave spectrophotometer, as described in the WO 92/20273
5 publication published November 26, 1996, now pending as U.S. patent application serial no. 08/150,084, which is incorporated by reference as if fully set forth herein. Alternatively, spectrophotometer unit 20 is a time resolved spectrophotometer, as described in the U.S.
10 Patents 5,119,815 and 5,386,827, or a phase modulation spectrophotometer, as described in the U.S. Patents 4,972,331 and 5,187,672, and in the co-pending U.S. patent application 08/031,945 all of which are incorporated by reference as if fully set forth herein.

15 Stimulation unit 30 is constructed to stimulate a specific neural function of a subject. The stimulator, controlled by computer 40, emits mechanical, electrical, thermal, sound or light signals designed to stimulate the neural activity of interest. The neural activity is
20 induced by sensory stimuli, such as visual, auditory, or olfactory stimuli, taste, tactile discrimination, pain and temperature stimuli, or proprioceptive stimuli.

In a first preferred embodiment, a continuous wave spectrophotometer includes several sources and detectors
25 attached to the optical module mounted on the head of the examined subject. Referring to Fig. 2, optical module 12a includes twelve light sources S1, S2, ..., S12 and four light detectors D1, D2, D3, and D4 mounted on a plastic material. The light sources and the light
30 detectors are located on a geometrical pattern that provides sixteen source-detector combinations (C1, C2, ..., C16) having a selected source-detector separation. The separation was selected to be 2.5 cm, which produces about 1.25 cm average light penetration, to obtain a two
35 dimensional image of the cortical surface. The light

- 15 -

charging current in the first step. This is achieved
using an appropriate ON/OFF combination of switches A and
B. The voltage of capacitor 58 is charging to a value
which, after 200 msec., represents the total detected
5   intensity minus the dark level noise signal. In the
third step, both switches A and B are turned OFF to
disconnect both the positive unity gain and the negative
unity gain operational amplifiers (60 and 62). Then, the
output of integrator 58 is moved via switch C to an
10   analog-to-digital converter and the digital signal is
stored in the memory of computer 60. In the fourth step,
the switches A, B and C are open and switch D is closed
in order to discharge capacitor 58 through a 47K
resistor. At this point, the circuit of integrator 56 is
15   reset to zero and ready for the first step of the
detection cycle.

Alternatively, analog circuit 50 may be replaced
by a computer with an analog-to-digital converter and
appropriate software that controls the entire operation
20   of optical module 12A. For instance a source code and be
written in C language, to control the sources and the
detectors of optical module 12A in a similar way as
described above. The detected dark level noise signal is
digitally subtracted from the detected intensity of the
25   introduced light. A program can also be readliy written
to transfers the raw data file, written in C, to another
format for further use by the imaging algorithm.

This optical tomography system was used to image
the activity of the visual cortex of a 54 year-old male
30   subject while strictly observing the established safety
protocol. Optical module 12A was placed on the occipital
bone of the skull to observe the surface of the occipital
cortex. A first data set was acquired for all sixteen C1
through C16 combinations with the subject having his eyes
35   closed. A second data set was collected while the

of the parietal cortex. Similarly as above, a first data set was acquired for all sixteen C1 through C16 combinations with the subject having his fingers in rest. A second data set was collected while the subject was
5 tapping as fast as possible for about 40 seconds, and a third data set was acquired after a rest period of 30 seconds. A fourth data set was acquired after a rest period of 30-60 seconds. Figs. 4A, 4B and 4C depict differential images of blood volumes of the motor cortex
10 of the subject man tapping his fingers, after a rest period of 30 seconds, and restored rest volumes at 30 - 60 seconds, respectively. The images show an increased blood volume, which is accompanied with desaturation of hemoglobin in the imaged area.

15   In another experiment, the optical tomography system was used to image the cognitive activity in the prefrontal cortex of a subject. A high school student was asked to translate words from English to French for 40 seconds with resting periods of 2 minutes. Figs. 5A,
20 5B and 5C depict differential images of the hemoglobin oxygenation of the prefrontal cortex of a man translating words from English to French during three successive periods of 40 seconds. In an area of 0.5 x 2 cm of the prefrontal cortex, the images show repeated increased
25 blood oxygenation due to the activation in a specific part of the cortex. However, the first image of the first stimulus produced the highest oxygenation increase. Similarly, Figs. 6A, 6B and 6C depict differential images of the blood volumes in the same area of the prefrontal
30 cortex during the translation from English to French.

     In another important embodiment, a three dimensional image is created by producing slices of the above described two dimensional image at different depths of average photon penetration. The optical module
35 includes a hairbrush optical coupler disclosed in the PCT

- 19 -

The optical module is constructed to maintain a
selected separation of the input and detection ports. In
a reflection geometry, the photons of the introduced
light migrate over a "banana" pattern with an average
5 penetration depth about one half on the input-detection
port separation. Thus, a neural region is targeted by
the location and separation of the ports of optical
module 12. The exterior locations of the ports depend on
the targeted neural region. The locations of the neural
10 regions have been extensively mapped in the prior art and
are known to a person skilled in neuroanatomy and
neurophysiology.

The computer uses a backprojection algorithm known
in computed tomography (CT) modified for light diffusion
15 and refraction and the banana like geometry employed by
the optical imaging system. In the optical
backprojection algorithm, the probabilistic concept of
the "photon migration density" replaces the linear
relationship of ballistically transmitted X-rays, for the
20 beam representing pixels. The photon migration density
denotes a probability that a photon introduced at the
input port will occupy a specific pixel and reach the
detection port. For different types of tissue, the phase
modulation spectrophotometer provides the values of the
25 scattering and absorption coefficients employed in the
probability calculations. In the image reconstruction
program, the probability is translated into a weight
factor, when it is used to process backprojection. The
backprojection averages out the values of information
30 that each beam carries with the weighting in each pixel.
The specific algorithms are embodied in the source code
provided in Appendices E and F. Appendix E is a source
code that incorporates a weighting algorithm for creating
a photon density image used in the backprojection
35 reconstruction algorithm disclosed in Appendix F.

- 21 -

oculocephalic reflexes, oculovestibular reflexes, deep
tendon reflexes, abdominal reflex, cremasteric reflexes,
postural reflexes, gag reflex, infantile reflexes (such
as blinking reflex, cochleopalpebral reflex, palmar grasp
5   reflex, digital response reflex, rooting reflex, Galant's
reflex, tonic neck reflex, Perez reflex, startle reflex).
      The stimulator stimulates a selected region of the
nervous system. The corresponding neurologic impulses,
transmitted by the neurons, are detected and imaged at
10   different points of their paths, for example, in the
nerves, in the spinal cord, in the thalamus, or in the
cerebral cortex. For example, when the stimulator causes
a cold or hot stimulation on the little finger of the
left hand, this thermal stimulation produces impulses
15   that travel in the right lateral spinothalamic tract of
the cervical spinal cord, to the thalamic sensory nuclei
and end in the right postcentral gyrus of the parietal
lobe.

      What is claimed is:

- 23 -

2.   An optical system for in vivo, non-invasive
functional neuroimaging of tissue comprising:

a stimulator constructed to stimulate a selected
functional activity of neural tissue of interest;

5   an optical module including an array of input
ports and detection ports located in a selected
geometrical pattern to provide a multiplicity of arrayed
single source, single detector pairs engaged directly
with the subject;

10   a spectrophotometer including

light source means constructed to introduce
electromagnetic radiation of visible or infra-red
wavelength into the examined neural tissue successively
at the input ports, the wavelength being sensitive to a
15 tissue constituent associated with a physiological
response of the imaged functional activity;

detector means constructed to detect, at said
detection ports, radiation of the selected wavelength
that has migrated in the stimulated neural tissue from
20 respective input ports; and

a processor receiving signals of said detected
radiation from said detector means, and constructed and
arranged to create a defined spatial image of the
functional activity of neural tissue by effectively
25 producing from the signals from the multiplicity of
arrayed single source, single detector pairs, a first
data set representing, from a selected view, a spatial
image of the neural tissue at rest, a second data set
representing, from the same selected view, a spatial
30 image of the neural tissue during stimulation, and a
functional image data set that is related to the
differences between said first and second data sets, over
said sets.

- 25 -

10.   The optical system of claim 2 wherein said stimulator is constructed to stimulate the cognitive cortex.

11.   The optical system of claim 2 wherein said
5   stimulator is constructed to stimulate the sensory motor cortex.

12.   The optical system of claim 2 wherein said stimulator is constructed to stimulate spinal tissue.

13.   The optical system of claim 2 wherein said
10 stimulator is constructed to deliver electrical signals to selected tissue.

14.   The optical system of claim 2 wherein said stimulator is constructed to apply an electrical field to selected tissue.

15   15.   The optical system of claim 2 wherein said stimulator is constructed to deliver magnetic signals to selected tissue.

16.   The optical system of claim 1 or 2 wherein said image set is related to at least one of the group
20 consisting of blood volume, hemoglobin oxygenation or deoxygenation, photon absorption coefficient, photon scattering coefficient, refractive index, change in magnetic field, change in electric field, production of or change of a specific tissue constituent, and
25 production of or change in the concentration of a pigment.

17.   The optical system of claim 1 or 2 wherein said tissue constituent is an endogenous pigment.

- 27 -

23. The optical system of claim 22 further comprising

a second oscillator constructed to generate a second waveform at a second frequency;

5   said detector means arranged to receive a reference waveform at a reference frequency offset by a frequency on the order of 10^3Hz from said first frequency and to produce a signal, at said offset frequency, corresponding to said detected radiation; and

10   said phase detector adapted to compare, at said offset frequency, the detected radiation with the introduced radiation and to determine therefrom the phase shift at said wavelength.

24. The optical system of claim 1 wherein said
15 spectrophotometer includes

a light source, means constructed to generate pulses of radiation of said wavelength, said pulses having duration on the order of a nanosecond or less;

said detector means being constructed to detect
20 over time photons of modified pulses that have migrated in the tissue from said input ports;

an analyzer, connected to said detector means, adapted to determine a change in the pulse waveform shape of said detected pulses relative to said introduced
25 pulses, at said wavelength; and

said processor being constructed and arranged to create said image data set based on said determined pulse waveform change.

25. The optical system of claim 24 wherein said
30 processor is constructed and arranged to calculate the effective pathlength of photons of said wavelength migrating between said input and detection ports in conjunction with creating said image data set.

31. An instrument for functional imaging of brain activity of a subject comprising a brain imager, including an array of sources and detectors defining a multiplicity of source-detector pairs, constructed and
5 arranged to image hemoglobin, deoxyhemoglobin or blood volume at depth within the brain during administration of a respective stimulus to the subject, said brain imager including

a processor receiving signals of said detected
10 radiation from said detector, and constructed and arranged to create a defined spatial image of the functional activity of neural tissue by effectively producing a first data set representing, from a selected view, a spatial image of blood in the cortex while the
15 subject is at rest, a second data set representing, from the same selected view, a spatial image of the blood in the cortex during stimulation, and a functional image data set that is related to the differences between said first and second data sets, over said sets.

20   32. The device of claim 31 in the form of a near infrared hemoglobinometer based on introducing and detecting photons that have migrated through tissue of the head.

        33. The device of claim 32 having multiple
25 source-detector pairs for engaging the skull, the source being spaced from the detector for selected pairs between about 1.5 and 7 cm.

        34. The device of claim 33 in which the spacing is 2.5 cm or greater.

- 31 -

38. An instrument for functional imaging of brain
activity of a subject comprising an imager constructed
and arranged to image hemoglobin, deoxyhemoglobin or
blood volume, said imager comprising

5   an array of sources of near infrared or visible
photons,

        an array of detectors positioned to receive
photons from the sources following migration of photons
from the sources through the tissue,

10   a system enabling numerous readings of migrated
photons to be taken systematically for different source-
detector positions relative to the tissue, and

        a processor employing data sets taken during rest
and during stimulation, with an imaging algorithm that is

15 based on respectively different probabilities for a given
source-detector position, for photons from the source
passing through different regions of the volume of the
scattering tissue that are located at different positions
distributed laterally from a straight reference line

20 between source and detector.

39. The imaging instrument of claim 37 or 38 in
which the imaging algorithm is a back-projection
algorithm, and said probabilities are implemented as
respectively different weight factors employed in the

25 algorithm for detected energy for different pixels of the
image.

40. The instrument of claim 31, 37 or 38
constructed to store at least one set of data for a given
area of the brain while the subject is at rest and at

30 least one set of data for the given area of the brain
while the subject is stimulated, and to produce a defined
output image representing the differences over the area
of the respective sets of data.

- 33 -

47. The method of claim 46 including introducing
an optical contrast agent or a drug to the blood stream
of the subject, and

        producing with the instrument an image data set
5 for the tissue while the contrast agent or drug is
   present in blood circulating in the tissue of the subject
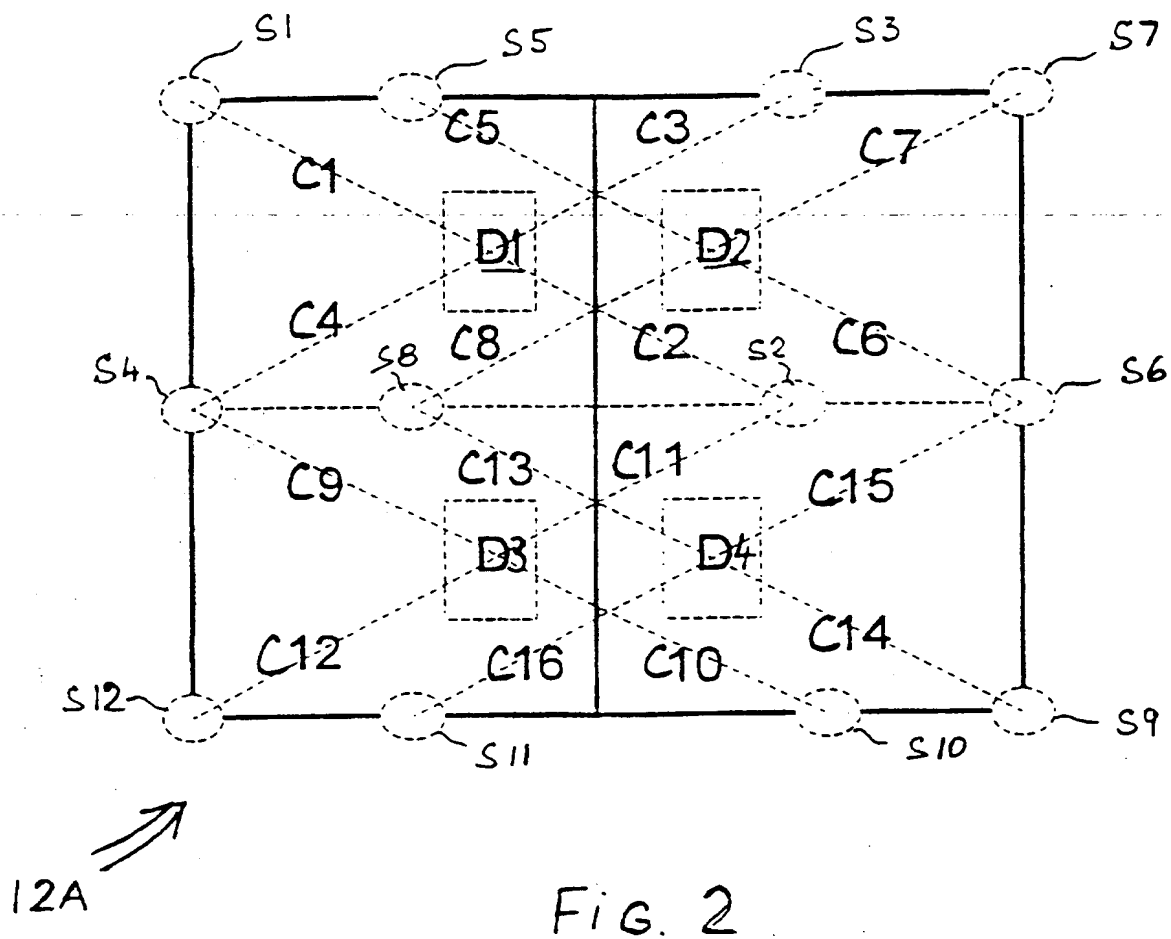   or is present in the localized tissue.

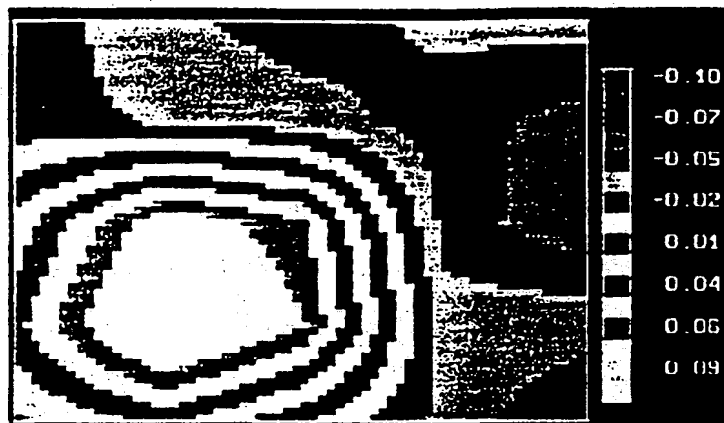FIG. 2

FIG. 3A

FIG. 3B

FIGS. 5A   5B   5C

FIGS. 5A   5B   5C

Interr...ional Application No

PCT/US 97/16309

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6   A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6   A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
29 January 1998	10/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Chen, A

Form PCT/ISA/210 (second sheet) (July 1992)

2

page 1 of 3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 88 01485 A (SINGER) 10 March 1988 see abstract see page 11, line 7 - page 13, line 20 ---	5,24,30, 37,39,41
A	US 4 940 453 A (CADWELL) 10 July 1990 see column 7, line 11 - column 8, line 54 see figures 2-4 ---	11,13-15
A	US 5 143 081 A (YOUNG ET AL.) 1 September 1992 see column 17, line 4 - line 45 -----	12

2